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Vaccine Safety: An examination of the value and necessity of Phase III trials

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Abstract

Phase III trials of vaccines may be holding back the benefits of, and increasing the costs of vaccines, to an extent that is harmful to society. The safety of a vaccine is assessed, in the main, in Phases I and II trials. Were Phase III trials to be rendered unnecessary, it would be desirable to more extensively and stringently examine the performance of the vaccine in the field as part of a post licensure Phase IV exercise. The acceptance of such costs (risk of disbenefit * the magnitude of the disbenefit) is discussed in relation to costs that are commonly incurred while engaged in a modern 21st century life.

Keywords: Phase III vaccine trials; vaccine safety; risk; cost; benefit

1. Introduction

Hardly a week goes by without a major article appearing on the front pages of a national newspaper proclaiming the possible implication of a vaccine in damaging a previously healthy vaccinee. This is a consequence of both the widespread use of vaccines and the sensitivity of the public to the risk of vaccine caused damage to the health of a vaccinated individual. A corollary of this state of affairs is that the authorities who possess the right to licence a vaccine for general sale and distribution are extremely cautious in their granting of such licences. Indeed, their degree of caution can be envisaged by their requests for repeated testing of the vaccine that may take between 5 and 25 years at a cost of some $800-1000 million [1] and could involve hundreds of thousands of test subjects. The question that will be examined in this paper, is whether or not this test procedure is necessary, excessive and in any way contributory to the distribution of the safest vaccines that can be produced?

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It is well recognised in the pharmaceutical industry that vaccines leading to prophylaxis and the prevention of disease are expensive to produce. This statement is supported by the comparing the global income to the industry from sales of all pharmaceuticals in the year 2007 - $712 billion with the global sales of vaccines in the same year - $20 billion. It should also be noted that across the pharmaceutical industry the proportion of their research and development funds devoted to research in prophylaxis is about 8-12% of the total research budget of these companies. This means that for about 10% of research expenditures there is a return to the companies of some 2.8% of the revenues. This disproportionation may be seen as a direct result of the seeming necessity for the exhaustive testing of the vaccine before the companies can release it to the market and receive a fair return on their endeavours.

There are two consequences to this state of affairs. The first is that when first released into the market place the cost of a dose of the vaccine is set so as to recoup the costs of the process that led to its being. This means that the 8+ hundred million dollars spent in the testing phase has to be recouped before the patent protecting the invention for the company runs out of time. So it is hardly surprising that instead of costing about $1 per dose [this figure is charged for vaccines that are out of patent and have been in the field for decades] typically a dose may cost between $50-150.

This makes a new vaccine expensive. It also means that when a health care system is allocating its funds and effects a cost-benefit calculation on the use of a new vaccine, it is likely to reject the vaccine because the cost of procuring a year of active life is larger than the value attributed to that year of active life. This means that the vaccine does not get used and the people who would have benefited from the prevention of a disease state will now suffer the disease and may even die as a result.

A second consequence of the current testing regimen is that the vaccine does not become widely available for many years whilst it is in the throes of the regulator bodies [typically 2-10 years [1]] . Here again we can expect that many people will be denied the prophylaxis that will maintain their state of good health. Some will suffer; some will die.

It is clear that the cost of the regulatory regimen that requires such exhaustive testing before the granting of a licence to produce and sell a new vaccine may well be higher than any benefit that would result from a vaccine that is safer than it would have been were this testing obviated. Indeed the case can be made that ***during the extensive Phase III trials that are responsible for these considerable expenditures, there is not any increase in the safety of the vaccine.*** So, why should we continue to do them?

[It is well to note that the vaccine that goes into the market with a licence is generally the one that emerges from the Phase II trials that assess safety, consistency of the production system and efficacy. It would be unwise for a vaccine producer to enter into the expensive, time consuming and complex Phase III trial if the producer was not confident that the vaccine would pass the trials.]

1.1. The Safety of Vaccines is dealt with before Phase III

In the development of a new vaccine, the researchers seek to identify an immunogen which, when presented to a subject, creates as state of immunity in that individual [human and animal] that protects against infection with the pathogenic congener of the immunogen. Most of the preliminary experiments are effected in animals; typically mice and where necessary, non-human primates – generally monkeys. There is a route whereby, if immunogenicity is demonstrated in mice or other rodents, the experiments progress to monkeys before humans are brought into the picture. During the course of these experiments the investigators are mindful of both the immunogenicity of the putative vaccine as well as any harmful reactions that the vaccine induces in the test subjects. They are also keen to explore and discover the

mechanism of action of the test material so that they can further reassure themselves of both the basis for the efficacy of the immunogen and its capability of causing harm. This latter effect has to be interpreted carefully. On the one hand it is necessary for the test immunogen to cause an immune response. This will change the state of the immune system. Some effects of this change of state may be that there will be reactions both at the site of application of the putative immunogen and more generally. Redness, swelling, soreness, stiffness, temperature rises and headache are not uncommon but are at low levels and are generally tolerated by the test vaccinees. [In animal experiments, animals that are clearly in pain are euthanized using standard, specified and Ministry regulated humane methods.]

So, before the test vaccine is allowed into humans [except for the possible inoculation of "named patients" who receive test materials free of charge] the putative vaccine has been thoroughly tested in a variety of animals over a period of a year or two. During this time the vaccinologist has developed a sense of how much immunogen to apply, where to apply it, how many doses are needed and which adjuvants may be used to boost the immunogenicity and broaden the range of the vaccine's efficacy. It is time to test the new test vaccine in humans.

1.2. Testing the vaccine in humans is presently done in 4 phases.

Phase I : some tens to a few hundreds of humans may be "vaccinated" to show that the vaccine is safe to use more widely. An indication of the effect of dose size on reactogenicity is determined and a dose regimen is set so as to obtain a well tolerated reaction.

Phase II: should the tests effected in Phase I clearly demonstrate that further use of the vaccine is unlikely to cause undue harm, then the vaccine is applied to several thousand individuals who are chosen as the most likely to benefit from such a vaccination. In this Phase II the dose of the vaccine is ascertained as is the method of application and the effect of multiple doses. The effectiveness of the vaccine at this time is determined by measuring those parameters of the vaccinated individuals that have been found in the previous animal testing to most closely correlate with an immune state to a challenge with the appropriate pathogen. In short, this Phase II is the real safety test of the vaccine because should there be any untoward reactions observed during this closely monitored test period then this vaccine does not proceed further into what is Phase III. So, by the end of Phase II the investigators have arrived at an acceptably safe vaccine that is clearly of a significant and known degree of efficacy.

Phase III: In this phase the vaccine is applied to several tens to hundreds of thousands of subjects one or several times in different situations that fully represent the range of individuals who are likely to be the beneficiaries of the vaccine. For this test in the field, there is normally a vaccinated group and an equivalent group that is exposed to a preparation that does not contain the immunogenic material – the placebo group. This then tests how the vaccinated individuals stand up against the natural threat of infection posed by the pathogens that abound in nature when compared with the control group that are not really vaccinated. The number of subjects required for this trial is determined by the natural rate of infection. If only one person per 1000 individuals is normally infected by natural means, then it is clear that a significant test of the vaccine has to include many thousands of such people in order to see a clear difference between the vaccinated group and the control, or placebo vaccinated, group. [Neither the vaccinees nor the vaccinators know whether those receiving an injection are vaccinated or are a member of the placebo group.] While testing the vaccine for its efficacy in preventing disease, it is also examined from the point of view of its safety. Generally, nothing has been done to the vaccine to affect its safety. So the expectation would be that, failing the emergence of a surprising condition, the safety test of Phase II would be repeated with a larger number of people. And that is all. An increase in the safety of the vaccine is neither achieved nor attempted. The only statement that one may make is that as the vaccine has been more widely tested, there is a greater assurance that the level of safety observed in the previous

testing is a faithful representation of the actual safety of the vaccine. But this has not affected the safety of the vaccine in any way – only the way a certain set of regulators have their minds set at a greater degree of ease. – ***But at what cost ?***

Additionally, it would be expected that the vaccine to be used in the Phase III tests would be the same vaccine that would go into the population in the post licensure situation. This means that at least three lots of vaccine would have been made to a standard that shows the consistency of the production process under the Good Manufacturing Procedures that are required by the Regulatory Agencies.

The elimination of the Phase III trials is precedented. The annual influenza vaccination does not go through these trials as it is held that previous experience and the ability to measure antibodies induced by the vaccine as a correlate of protection serve to provide confidence that the current year's vaccine is equivalent in its immunogenicity to previous such like vaccines. These arguments also applied to the introduction of a Meningococcal C vaccine in the UK and also to a Pneumococcal vaccine [2].

Phase IV: The vaccine has now been licensed for general use. The manufacturer sells it into the market place – the testing has not yet been completed. It never is. Whenever a vaccinee reports a severe adverse event [SAE] in close temporal relationship to having been vaccinated and such that it requires that individual to go to seek medical advice the regulatory authorities are informed and begin to compile a dossier on the safety of the vaccine in general use in the field. In effect, this is the real safety test of the vaccine. It is expected that individuals come down with a variety of diseases in the normal course of events. The timing of the ecrudescence of a disease may coincide in time with being vaccinated. This does not mean that the vaccine has caused the disease, but it is difficult to convince a public that does not expect vaccines to cause serious damage to vaccinees to accede to that reality.

As it is clear that when a vaccine is in general use, it, and all other products that can cause harm such as cars, electrical appliances, ladders, drugs etc., are under a universal surveillance for their safety. So may not this Phase IV serve as the safety test that was required in Phase III?

Were the regulatory authorities to accept that Phase III does not lead to any increase in vaccine safety, and that safety is fully monitored throughout the use of the vaccine in the field, there is not any justification for the implementation of Phase III testing with the corollary that the vaccine will get out into the field quicker thus preventing disease and death that would not otherwise have been, and **it would cost a great deal less** so that vaccines would be priced at a level that would make them attractive to be taken up by health authorities as the cost-benefit calculation would come out in favour of vaccine use: to the considerable benefit of all.

1.3. Other benefits from the elimination of Phase III testing.

1. Cheaper vaccines render themselves available to people from the developing and under developed world. Indeed this is where much of the disease that threatens us all abounds. It also means that the poor of these regions would be freed from much of the disease that binds them to the conditions of poverty. It also means that when they loose the fear of the death of their children they may have fewer children and so be in a position to take benefit from rising standards of living that are free from the threat of erosion due to increases in the population. It also means that females can be educated which is one of the most potent ways of achieving sustainable population levels.

2. At present, only organisations that have the means to financially pay for the Phase III trials are enabled to seek to produce vaccines for humans. This has the effect of requiring the new and small biotech companies that are pioneering many of the imaginative approaches to new vaccines to sell out to

those organisations that can fund the expensive Phase III trials. The elimination of the Phase III requirements would unleash the real potency of the new and keen companies who seek a place in the scheme of things. There would be a resurgence of activity in the production and testing areas as well as in the opening up of business and investment opportunities.

3. Were there to be an efflorescence of activity in the production and use of new vaccines, we might expect that there would be beneficial consequences to health care systems all round. The decrease in the disease burden and the number of people requiring medical attention would decrease the costs of health care which would enable the emergence of health care systems that are affordable and do not impugn the wealth of the society. Of course the sequellae to this would not work to the financial advantage of those in the pharmaceutical, medical, hospital, insurance and medico-legal areas. But then the people working in these areas have created a juggernaut that is engulfing a large and growing share of the national wealth. Cheaper, more varied and more available vaccines should eat into this runaway drain of national resources.

4. It is becoming ever more clear that the new oil-saponin-detergent-particulate adjuvants for experimental [and some approved by the European Medical Agency] investigation have clearly shown their power in potentiating the efficacy of vaccines – even so far as to make otherwise unefficacious vaccines, efficacious in elderly people who need protection from influenza and respiratory diseases caused by bacteria. These new adjuvant systems also broaden the range of efficacy so that protection is provided to more related strains and subtypes of common pathogens such as Influenza. The introduction of these new adjuvants into the American market seems to be prevented by a regulatory agency which either does not appreciate the value of such materials or is dubious of the safety of these materials. The fears of promulgating unsafe vaccines cannot be justified as many millions of doses of such adjuvanted vaccines have been used in Europe since 2002 to good effect and without any suggestion that the safety of the vaccines has in any way been compromised.

Safe Vaccines do not exist: How may we deal with this when we advocate the use of a vaccine.

It is a truism to state that there is nothing in this world that cannot cause harm to humans – and that includes water, air, animals, plants, humans and products made by humans such as vaccines. Nevertheless, we are faced with a public who are encouraged by the media to expect that there is not any downside harm that results from taking a vaccine. We are well aware that all people are different. Their immune systems are unique to themselves as persons. Some have immune systems that do not function – the immunocompromised. Others are on drugs that suppress or change the functioning of the immune system. And we are learning that individuals who express particular HLA molecules on the cells of the immune system may or may not respond to stimulation by particular vaccines [3].

It is also the case that when each individual in a population is vaccinated, extra protection is extended to those individuals in whom the vaccine “did not take” [for reasons given in the previous paragraph] through the “herd effect”. However, there is a significant minority of individuals who object to being vaccinated for a wide variety of reasons [4,5,6]. This author has suggested that people who wish to opt-out from vaccination programs with the full knowledge that they will be protected by their neighbours who have been vaccinated, should make some contribution to the community to compensate for having received a benefit [by not exposing themselves to the slight risk of vaccination damage while receiving a lower challenge to their immune systems from the disease protected people with whom they associate] without making a payment.

[The actual risk of harm from the commonly used vaccines is vanishingly small. Data from the Vaccine Compensation Injury Board of America – which is almost identical to that for similar boards in

England and Germany – shows that there is about one [7] successful claim for compensation for an alleged [but not fully investigated so that the discomfort experienced could be coincidental rather than caused by the vaccination] vaccine caused serious medical condition for each 1,000,000 doses of administered vaccine.]

1.4 The acceptability of exposure to a harm

This generates a new question. How may we so educate the public at large that they come to appreciate that the benefits of vaccination may only be achieved if they are prepared to accept a miniscule cost – albeit that such a cost is in terms of the pain and suffering [or even death] of a particular individual ?

The acceptance of damage by the public of most democracies depends on the circumstances. They will not object to the commitment of a high proportion of their young men and women to the protection of the society against the depredations of an aggressor. They are prepared to send the same young people to foreign lands to achieve the protection of the homeland by the curtailment of a foreign based terrorist operation. They actively encourage their young people to engage in sports where physical damage and even death is not uncommon – equine sports are one of the most dangerous with cycling, skiing and motor cycling in leading positions also. So, members of our publics are not unused to balancing costs [in human lives] against benefits [again in human lives] but also in strategically important economic or physical gains. To demonstrate this under controlled conditions, Philippa Foot [8] propounded “The Trolley Problem”. In this she asked test individuals how they would respond if they were in charge of the setting of the points of a railway line in the face of an approaching train that could either run into a group of, say, 5 workers on the line who were ignorant of the trains approach or would they reset the points to send the train down a branch line where it was known that a single individual was harnessed to the rails. In essence the individual with the power of controlling the points was asked if he or she would act to achieve the necessary death of a single individual to save the necessary deaths of several individuals. There are many variants of this problem. Not surprisingly, after many experiments with actual human subjects, the person who was in control of setting the points would activate the points to save the group more often if the group that would be saved was larger. Some 50% of people would be prepared to kill a single individual to save 2 people, while about 70% would be prepared to save 10, and 80% would save over 100 and up to 1000. The clear message is that there are some 20% of people who would not be prepared to take any action if it meant killing a single individual in the full knowledge that by doing nothing 1000 people would die otherwise. [9]

This poses a dilemma. It is not that the public is unwilling to make sacrifices of their near and dear ones to achieve ends that they accept. They are also mindful of the benefits of good health and they know that vaccines [along with the introduction of water cleaning and purification methods] have been the main providers of the high standards of health we enjoy today in the developed world and increasingly in the developing world. Yet they are reluctant to accept almost any cost in human terms to achieve this latter end. Why?

1. We could be [albeit highly unlikely] clearly guilty of a sin of commission when we apply a vaccine to an otherwise healthy individual. People do not like to be the personal purveyors of harm.

2. Vaccines, unlike cars, cigarettes, alcohol, guns and knives actually prevent people from acquiring disease. In some minds this thwarts the will of a deity who dispenses disease in response to the quality of the behaviour of individuals.

3. People do not like the physicality of the vaccination procedure that involves being injected using a syringe and needle.

4. Some societies on occasion have made vaccination obligatory. People object to laws that require them to be exposed to a hazard if they do not think they need what that exposure provides. They happily expose themselves to the dangers of motoring, that kills some 43,000 people per year on the roads of the USA and smoking that kills 400,000 per year because they want what motoring and smoking bring to them. They find it harder to want **future** good health because they already have it in the here and now.

5. Vaccination must be presented to people as an insurance event. We pay now for a future benefit.

[When calculating the benefits from insurance claims on properties or possessions the further into the future one proceeds the more the value of what is claimed is discounted. A car may insured for $10,000 in year one but the insurer will only provide $1,000 if the car reaches the age of 10 years. While many apply this rule to discounting the future value of vaccines, it may well be wholly inappropriate to use a discounted value for the health gain in the future. With medical costs increasing faster than the rate of inflation, the value to the individual of not having to pay a medical bill at a future date is of greater value than when he or she was vaccinated.]

Of course at the time of vaccination the vaccinee has no idea of what future disease they will be spared with its corresponding benefit. All that might be known is that over the society as a whole, if all become vaccinated there is likely to be a calculable benefit that is much greater than any costs incurred by all the vaccinations.

6. A vaccine manipulates the immune system of the vaccinee. People do not like to be affected in this way. It may be imagined to be a reconstruction of a body part – something that is welcomed for cosmetic purposes but not necessarily for the achievement of a state of immunity. A drug taken to relieve a painful condition results in a decrease in discomfort and is not dependent on a lasting change to the physicality of the body to achieve this end [normally, but not always].

7. People often feel that by taking the vaccine they are being compelled to add to the already large profits of the vaccine manufacturers.

1.5 Conclusion

So, while issues of safety do obtrude into the thinking of a person who is disinclined to be vaccinated they are not the only issues. It may be held that the people who support the anti-vaccine movement do not change the way they think about a vaccine when data purporting the vaccine's generally acceptable safety characteristics are published. For example, numerous trials on the safety of the measles component of the MMR vaccine have shown that there are not any outstanding safety issues with this vaccine; yet many people are not persuaded to take the vaccine as vaccination rates languish in the 80% region where once they were in the 90% area in the South East of the UK.

It may well be that were the costs of the vaccine to the society and the consumer be radically lowered, some, if not all, of the heat of those who object to vaccines and vaccination will be laid to rest. This can be achieved through bye-passing Phase III testing and seeking to achieve the same information by carefully and thoroughly by watching the performance of the vaccine as it is in use.

Should there be any safety issues the vaccine may be withdrawn without further ado, [as it was in the case of Rotavirus in the USA in 2004 [10]]. Should the vaccine not achieve the levels of immunity required it may also be withdrawn or fortified by extra doses or increase levels of immunogen in the vaccine. All cases of "vaccine breakthroughs" will be thoroughly examined and explanations sought. To

achieve this Phase IV surveillance effectively and reliably, positive steps have to be taken to provide and enhance the existing monitoring, recording and diagnostic laboratory facilities that will enable the system to serve as a reliable back-stop in protecting populations against any unexpected and untoward effects of the introduction of a new vaccine.

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